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ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/872,349	PRESTKA	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of newly added claims 33-42 in the paper filed 1/5/04 is acknowledged. All of the claims are being examined as they relate to one group. As such the traversal is moot. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 33-42 are pending and under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 33-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 33-42 are indefinite for reciting “”at least 5 days of incubation of the phosphorylated form in animal serum or buffer” in claims 33, 35, 36 because it is not clear if the incubation is in vitro or in vivo or both or what the conditions are contemplated for measurement. What is the temperature? Is there a preincubation time?

B. Claims 33-42 are indefinite for reciting “other than a termini of the antibody” in claim 33 or “located at the carboxyl terminus of the antibody” in claim 34. The phrases are unclear because it is unclear if the “termini” are located in the linear amino acid

sequence or in the tertiary structure of the antibody. Likewise the phrase "carboxyl terminus" is indefinite for the same reason. Is the terminus in the linear amino acid sequence or in the tertiary structure?

C. Claim 41 is indefinite for reciting "hybrid" antibody because it is not clear what a "hybrid" antibody is. Does it have a label, a human Fc, etc?

D. Claim 42 is indefinite for reciting "an Fc fragment" because it is unclear how an antibody is an Fc fragment. An antibody can have an Fc region but can't be an Fc region.

E. Claim 34 is indefinite for reciting "located at the carboxyl terminus" because it is unclear how the claim can depend from claim 33 which recites "a position other than a termini" and be at the C-terminus.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 33-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds antigen that is engineered to contain a serine at position 224 or a kinase recognition site at the carboxyl terminus in the linear amino acid sequence in the constant region wherein at least 80% of the phosphate groups remains attached after 36 hours in serum or buffer in vitro, does not reasonably provide enablement for an antibody that does not bind antigen or an

antibody that is engineered to contain a kinase recognition site just anywhere other than serine at position 224, or any site wherein the phosphorylated form is protected from hydrolysis by intermolecular interactions with other amino acids, or any phosphorylated antibody wherein 80%-99% of the phosphate groups remain attached after 5 days in animal serum or buffer in vivo The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any phosphorylated antibody with a kinase site engineered at any position that is not a termini or at the c-terminus and does not bind antigen, or an Fc fragment of an antibody, or a site that is protected from hydrolysis by intramolecular interactions with other amino acids, wherein 80% of the phosphate groups remain attached after at least 5 days in animal serum or buffer in vivo. The specification teaches that structural distortions may result from the attachment of phosphate groups to antibodies (see page 64) and it is extremely difficult to get the

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crystal structure of an intact antibody (see page 62, line 25) and the phosphoserine at

position 224 in the new constructs is highly resistant to hydrolysis (see page 64, lines 25-26). The specification teaches constructs which all have SER224 as the kinase recognition site (see Table 1) and the molecules were stable in serum or buffer in vitro for 5-21 days (see Table 5) and the specification discloses that MAb-WW5 which has SER 224 had a biodistribution that was higher in tumors than in other tissue or blood after 168 hours in a mouse in vivo tumor model (see Table 9). The specification teaches that there was significant hydrolysis of the phosphate from Mab-chCC49K1 where the fusion was at the C-terminus and that the molecule MAb-chCC49-6P was 91-93% stable after 36 hours in serum or buffer in vitro (see page 64, lines 22-24 and Table 3). The specification does not enable any other kinase site other than SER 224 or other than at a C-terminus of the linear amino acid sequence in a heavy chain or engineering any site that is protected from hydrolysis by the interaction with other amino acids or any molecule that is stable for at least 5 days in vivo.

The claims encompass adding a kinase recognition site at any location that is not in a termini which broadly reads on addition to a CDR site or an antibody that is an Fc fragment (claim 42).

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs

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are critical in maintaining the antigen binding specificity and affinity which is

characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that an antibody as defined by the claims which may contain alterations in a CDR, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Further, a fragment of the heavy chain Fc can be any one of the constant regions (CH1-3) and also may be the hinge region. However, the language also reads on small amino acid sequences which are incomplete regions of the constant region of the antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed.

The claims are broadly drawn to adding a kinase recognition site to an antibody

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such that the phosphorylated form is protected from hydrolysis by intramolecular

interactions with other amino acids. The specification teaches that it is extremely difficult to get the crystal structure and as such the tertiary structure of an intact antibody. As evidenced from Harris et al (Biochemistry 36:1581-97, 1997) the crystal structure of an intact mab231 provides for the first time the structure of an mouse fc and the specification discloses that there are only two crystal structures of intact Mabs (see page 62). As such this is evidence of the unpredictability of determining the structure of an antibody and the difficult of such means that one skill in the art would not be able to determine if the phosphorylated form is protected from hydrolysis by intramolecular interactions because one would not be able to determine the tertiary structure of the antibody.

The claims are broadly drawn to an antibody wherein at least 80%-99% of the phosphate is attached after at least 5 days in vivo in serum or buffer, however the specification does not have any data demonstrating this. The specification discloses MAb-WW5 has a biodistibution that after 168 hours is higher for the tumor than other tissues in a mouse model of cancer, however there is no data indicating that 80%-99% of the phosphate groups are still attached as indicated in the claims. The difference between the MAb-WW5 and the MAb-CC49K1 could be the labeling of the molecule and the fact that more label is incorporated in the WW5 molecule as opposed to the CC49K1 molecule. In addition, the specification or the prior art does not teach a molecule wherein at least 95-99% of the phosphates are attached after at least 5 days in serum or buffer in vitro or 80% are attached in vivo that has a kinase site at the C-terminal. As evidenced from Lin et al (Protein Expression and Purification 15:83-91,

1999) a molecule that has a kinase site at the C-terminus showed that 93% was intact after 72 hours in vitro (see page 89). Thus, there is no indication that any molecule with a C-terminus kinase site would be stable and had at least 95-99% of the phosphates after at least 5 days in buffer or serum in vitro or in vivo.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 33-34, 37, 39-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al (Anticancer Res 18:3971-78, 1998).

The claims recite a phosphorylatable antibody engineered to include a kinase site at the carboxyl terminal wherein the phosphorylated antibody has at least 80% of the phosphate groups after at least 5 days in buffer and the kinase site is a site for a serine and is a casein kinase II site and the antibody is a humanized, chimeric monoclonal antibody. Because of the indefinite nature of the claims claim 33-34 is combined and interpreted as claiming an antibody with the kinase site in the carboxyl terminal. The art is applied to the part of the claims that are enabled, specifically an

antibody that has a kinase recognition site that is at least 80% stable for 36 hours in animal serum or buffer in vitro.

Lin et al teach the humanized chimeric antibody MAb-chCC49CKII that has a casein kinase recognition site engineered at the C-terminus of the heavy chain (see abstract and page 3972. Lin et al teach that 90% of the phosphate is attached to the MAb after 72 hours in buffer in vitro (see page 3974, right column).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 33-34, 37-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al (Anticancer Research 18:3971-78, 1998), as applied to claims 33-34, 37, 39-41 above, and further in view of Pestka (US Patent 5,986,061, filed 6/95).

Claims 33-34, 37, 39-41 and there interpretation have been described supra. Claims 38 and 42 recite wherein the recognition site is for a cyclic AMP dependent kinase or GMP or cyclic nucleotide independent kinase and the antibody is a Fab or Fab' fragment.

Lin et al has been described supra. Lin et al does not teach a Fab or Fab' fragment or a recognition site that is for a cyclic AMP dependent kinase or GMP or cyclic nucleotide independent kinase. These deficiencies are made up for in the teachings of Pestka.

Pestka teach proteins with a kinase recognition site engineered into the proteins or at the C-terminus and the sequences can be GMP, AMP, and other dependent and independent kinases and the proteins can be antibodies and Fab or Fab' fragments (see column 8-9, column 10, line 20-30, column 30, line 40-45, 66, column 33, lines 64-67 and claim 20).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have engineered any kind or kinase recognition site into the C-terminal of the Fab or Fab' molecule in view of Lin et al and Prestka.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have engineered any kind or kinase recognition site into the C-terminal of the Fab or Fab' molecule in view of Lin et al and Prestka because Pestka teach modified antibodies with a kinase recognition site engineered into them can be used for therapy and the recognition site can be for any protein kinase (see column 8) and the antibody can be a Fab or Fab' and these can be used because they

are multichained molecules (see column 30, lines 64-66). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have engineered any kind or kinase recognition site into the C-terminal of the Fab or Fab' molecule in view of Lin et al and Prestka because Lin et al teach a therapeutic antibody that has been engineered to have a kinase site and the molecule is stable in buffer invitro. Thus, it would have been obvious to use other kinase recognition sites in view of Pestka and use Fab or Fab' fragments because these molecules are recognized as therapeutic molecules and Prestka teach that the phosphorylation site can be introduced to the intact protein or appropriate fragments through genetic engineering (see column 31, line 57-60).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by

telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832